

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
19 September 2002 (19.09.2002)

PCT

(10) International Publication Number
WO 02/072636 A3

(51) International Patent Classification: **C07K 16/00**,
A61K 39/395, G01N 33/53, A61K 47/06, 47/36, 47/38,
47/42, A61P 35/00, G01N 33/569

(21) International Application Number: PCT/US01/49628

(22) International Filing Date:
26 December 2001 (26.12.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/258,704 28 December 2000 (28.12.2000) US

(71) Applicant (for all designated States except US): **ALTUS
BIOLOGICS INC.** [US/US]; 625 Putnam Avenue, Cam-
bridge, MA 02139-4807 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **SHENOY, Bhani**
[US/US]; 16 Westgate Drive, T-6, Woburn, MA 01801

(US). **GOVARDHAN, Chandrika, P.** [US/US]; 9 Scot-
land Road, Lexington, MA 02420 (US). **YANG, Mark,
X.** [US/US]; 59 Bridge Street, Newton, MA 02458 (US).
MARGOLIN, Alexey, L. [US/US]; 193 Upland Avenue,
Newton, MA 02161 (US).

(74) Agents: **PIERRI, Margaret, A.** et al.; c/o Fish & Neave,
1251 Avenue of the Americas, New York, NY 10020 (US).

(81) Designated States (national): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,
CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,
MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG,
SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ,
VN, YU, ZA, ZM, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR,
GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent

[Continued on next page]

(54) Title: CRYSTALS OF WHOLE ANTIBODIES AND FRAGMENTS THEREOF AND METHODS FOR MAKING AND USING THEM

Rituximab Crystals



(57) Abstract: Methods are also provided for preparing stabilized formulations of whole antibody crystals or antibody fragment crystals using pharmaceutical ingredients or excipients and optionally encapsulating the crystals or crystal formulations in a polymeric carrier to produce compositions and using such protein crystals for biomedical applications, including delivery of therapeutic proteins and vaccines.



(BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR,
NE, SN, TD, TG).

(88) Date of publication of the international search report:
17 April 2003

Published:

— with international search report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 01/49628

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07K16/00 A61K39/395 G01N33/53 A61K47/06 A61K47/36
A61K47/38 A61K47/42 A61P35/00 G01N33/569

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

MEDLINE, EPO-Internal, WPI Data, PAJ, BIOSIS, CHEM ABS Data, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>HARRIS L J ET AL: "Crystallographic structure of an intact IgG1 monoclonal antibody." JOURNAL OF MOLECULAR BIOLOGY. ENGLAND 6 FEB 1998, vol. 275, no. 5, 6 February 1998 (1998-02-06), pages 861-872, XP002208332 ISSN: 0022-2836 abstract page 861, column 1, line 7 -column 2, paragraph 2 page 869, column 1, paragraph 6 -column 2, paragraph 1</p> <p style="text-align: center;">--- --/--</p>	1,4,11



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
 "E" earlier document but published on or after the international filing date
 "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
 "O" document referring to an oral disclosure, use, exhibition or other means
 "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
 "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
 "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
 "G" document member of the same patent family

Date of the actual completion of the international search

19 November 2002

Date of mailing of the international search report

12.12.02

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentian 2
 NL - 2280 HV Rijswijk
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
 Fax: (+31-70) 340-3016

Authorized officer

Montrone, M

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US 01/49628

C (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>WO 99 55310 A (MARGOLIN ALEXEY L ;RAKESTRAW SCOTT L (US); KHALAF NAZER K (US); SH) 4 November 1999 (1999-11-04)</p> <p>abstract page 1, line 4-12 page 1, line 25 page 2, line 3-32 page 3, line 26-33 page 8, line 20-33 page 9, line 10-29 page 10, line 1-28 page 14, line 4-27 page 15, line 11-16 page 16, line 3,4 page 16, line 27 -page 17, line 4 page 18, line 8-16 page 28, line 24 -page 29, line 13 page 29, line 14-18 page 30, line 18-26 page 36, line 22-29 page 37, line 16 page 39, line 31 page 41, line 1-12 page 51, line 22 -page 54, line 16 page 54, line 17-25 page 60, line 24 -page 61, line 24 page 66, line 26 -page 67, line 25 page 68, line 1 -page 69, line 7 page 71, line 1 -page 72, line 26 page 78, line 6 -page 79, line 5 page 81, line 25 -page 82, line 13 page 93, line 8 -page 94, line 16 page 112, line 15 -page 113, line 16 page 116, line 7 -page 118, line 18</p>	<p>1,4,11, 21-30, 32-68, 74-78</p>
X	<p>US 6 011 001 A (NAVIA MANUEL A ET AL) 4 January 2000 (2000-01-04)</p>	<p>1,4,11, 17,18, 21-23, 33, 40-42, 70-73, 76-78, 43-68, 74,75</p>
Y	<p>abstract</p> <p>column 3, line 10-60 column 10, line 14-19 column 11, line 11-22 column 28, line 54 -column 29, line 23 column 32, line 10 -column 33, line 2 column 33, line 33-47 column 34, line 27-62 column 47, paragraphs 41-52 column 49, line 38-56 column 55, line 51-54</p>	

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 01/49628

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>US 6 140 475 A (MARGOLIN ALEXEY L ET AL) 31 October 2000 (2000-10-31)</p> <p>abstract column 6, line 42-61 column 8, line 19 -column 9, line 67 column 10, line 42 -column 11, line 18 column 15, line 1-10 column 32, line 46-62 column 34, line 65 -column 35, line 16 column 39, line 14-32</p> <p>---</p>	<p>1,4,11, 21-23, 32-34, 39-68, 74-78</p>
X	<p>KÜTTNER G ET AL: "A phage library-derived single-chain Fv fragment in complex with turkey egg-white lysozyme: characterization, crystallization and preliminary X-ray analysis." MOLECULAR IMMUNOLOGY. ENGLAND FEB 1998, vol. 35, no. 3, February 1998 (1998-02), pages 189-194, XP002208333 ISSN: 0161-5890</p> <p>abstract page 190, column 2, paragraph 3 page 193, column 1, paragraph 5</p> <p>---</p>	<p>2,4,11</p>
X	<p>BRADEN B C ET AL: "X-ray crystal structure of an anti-Buckminsterfullerene antibody fab fragment: biomolecular recognition of C(60)." PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA. UNITED STATES 24 OCT 2000, vol. 97, no. 22, 24 October 2000 (2000-10-24), pages 12193-12197, XP002208334 ISSN: 0027-8424</p> <p>abstract page 12193, column 2, paragraph 2</p> <p>---</p>	<p>3,4,11</p>
X	<p>MYLVAGANAM S E ET AL: "STRUCTURAL BASIS FOR THE BINDING OF AN ANTI-CYTOCHROME C ANTIBODY TO ITS ANTIGEN: CRYSTAL STRUCTURES FO FABE8-CYTOCHROME C COMPLEX TO 1.8 Å RESOLUTION AND FABE8 TO 2.26 Å RESOLUTION" JOURNAL OF MOLECULAR BIOLOGY, LONDON, GB, vol. 281, no. 2, 14 August 1998 (1998-08-14), pages 301-322, XP001088724 ISSN: 0022-2836</p> <p>abstract page 302, column 1, paragraph 2 page 318, column 1, paragraphs 3,4</p> <p>---</p>	<p>3,4,11, 17,18</p>

-/-

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 01/49628

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>WO 00 52150 A (GENENCOR INT ; HENG MENG HONG (US)) 8 September 2000 (2000-09-08) abstract page 2, line 3-15 page 3, line 14-27 page 4, line 14-17 page 5, line 25-34 page 6; table 6 claim 1</p> <p>----</p>	43-68, 74,75
Y	<p>US 6 042 824 A (KHALAF NAZER K) 28 March 2000 (2000-03-28) abstract column 5, line 24-51 column 6, line 1-13 column 7, line 28-66 column 9, line 10-49 column 11, line 47-51 column 12, line 14-16 column 13, line 5-21 column 13, line 67 -column 14, line 4</p> <p>----</p>	43-68, 74,75
Y	<p>US 4 334 024 A (JOHAL SARJIT) 8 June 1982 (1982-06-08) abstract column 3, line 56 -column 4, line 3 column 4, line 14 -column 5, line 16</p> <p>----</p>	43-68, 74,75
Y	<p>WO 91 09943 A (NOVONORDISK AS) 11 July 1991 (1991-07-11) abstract page 2, line 1-30 page 4, line 17-23 page 5, line 15-23 page 10, line 14-16 page 11, line 1-15 page 12, line 15-19</p> <p>----</p>	43-68, 74,75
A	<p>BLANCO DOLORES ET AL: "Protein encapsulation and release from poly(lactide-co-glycolide) microspheres: Effect of the protein and polymer properties and of the co-encapsulation of surfactants." EUROPEAN JOURNAL OF PHARMACEUTICS AND BIOPHARMACEUTICS, vol. 45, no. 3, May 1998 (1998-05), pages 285-294, XP002221361 ISSN: 0939-6411 abstract</p> <p>-----</p>	1-4,11, 17,18, 21-30, 32-42, 70-73, 76-78

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 01/49628

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 40-42, 77 and 78 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the antibody crystals.
2. ☒ Claims Nos.: 5,7,16,31
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☒ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
1-4, 11, 17, 18, 21-30, 32-68, 70-78
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☒ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

Invention 1: claim 1 (complete), 4, 11, 17, 18,
21-30, 32-42, 70-73 and 76-78 (all partial)

Crystals of a whole antibody; Compositions and formulations thereof; Methods for use.

Invention 2: claim 2 (complete), 4, 11, 17, 18,
21-30, 32-42, 70-73 and 76-78 (all partial)

Crystals of single-chain Fv fragments of an antibody;
Compositions and formulations thereof; Compositions and formulations thereof; Methods for use.

Invention 3: claim 3 (complete), 4, 11, 17, 18,
21-30, 32-42, 70-73 and 76-78 (all partial)

Crystals of a Fab fragment of an antibody; Compositions and formulations thereof; Compositions and formulations thereof; Methods for use.

Inventions 4-48: claims 12, 19, 43-69, 74,
75 (all complete), 4, 6, 8-11, 13-15, 17, 18,
20-30, 32-42, 70-73, 76-78 (all partial)

Crystals of polyclonal, monoclonal, chimeric, humanised, non-glycosylated, bispecific, human, mouse, IgG, IgM, IgA, IgD, IgE, anti-idiotypic, Rituximab, Infliximab, Trastuzumab, Abciximab, Palivizumab, Murumonab-CD3, Gemtuzumab, Basiliximab, Daclizumab, Etanercept, Ibritumomab, anti-TNF, anti-CD3, anti-CD20, anti-CD25, anti-CD33, anti-CD40, anti-HER2, anti-HBV, anti-HAV, anti-HCV, anti-GPIIb/IIIa receptor, anti-RSV, anti-HIV, anti-HSV, anti-EBV antibodies; dried crystals of whole, single-chain Fv and Fab fragments. Compositions and formulations thereof; Methods for use. In addition, methods for large-batch crystallisation and for protein purification are considered to be separate inventions.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 5,7,16,31

Present claims 5, 7, 16 and 31 relate to a product defined by reference to a desirable characteristic or property, namely a crystal of a therapeutic antibody or an antibody used for the treatment of various diseases or the crystal is a carrier-free pharmaceutical controlled release crystal.

The claims cover all antibody crystals having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such crystals. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the crystal by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the crystals of an whole antibody.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No.

PCT/US 01/49628

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9955310	A	04-11-1999	
		AU 3764699 A	16-11-1999
		CA 2330476 A1	04-11-1999
		EP 1073421 A1	07-02-2001
		JP 2002512949 T	08-05-2002
		WO 9955310 A1	04-11-1999
		US 2002045582 A1	18-04-2002
US 6011001	A	04-01-2000	
		US 5618710 A	08-04-1997
		EE 3142 B1	15-12-1998
		US 5849296 A	15-12-1998
		US 5976529 A	02-11-1999
		US 6004768 A	21-12-1999
		US 5801022 A	01-09-1998
		NZ 264042 A	25-06-1996
		AU 662104 B2	24-08-1995
		AU 8315491 A	02-03-1992
		BR 9106732 A	17-08-1993
		CA 2087730 A1	04-02-1992
		CZ 9300123 A3	13-10-1993
		EP 0550450 A1	14-07-1993
		EP 0861888 A1	02-09-1998
		FI 930454 A	02-02-1993
		HU 65904 A2	28-07-1994
		HU 9500666 A3	28-11-1995
		IE 912767 A1	12-02-1992
		IL 99046 A	24-09-1998
		LT 1077 A ,B	25-04-1995
		LV 10304 A ,B	20-10-1994
		MD 1592 B2	31-01-2001
		NO 930360 A	02-04-1993
		PT 98564 A ,B	30-06-1992
		RU 2124052 C1	27-12-1998
		SG 70966 A1	21-03-2000
		SK 5993 A3	07-07-1993
		TJ 210 R3	14-11-1998
		WO 9202617 A1	20-02-1992
US 6140475	A	31-10-2000	
		AU 6966698 A	11-11-1998
		EP 0973878 A1	26-01-2000
		JP 2001523227 T	20-11-2001
		WO 9846732 A1	22-10-1998
		US 2002137156 A1	26-09-2002
		ZA 9803044 A	11-10-1999
WO 0052150	A	08-09-2000	
		AU 3393800 A	21-09-2000
		CN 1342198 T	27-03-2002
		EP 1159410 A1	05-12-2001
		WO 0052150 A1	08-09-2000
		US 6403350 B1	11-06-2002
US 6042824	A	28-03-2000	
		US 5932212 A	03-08-1999
		AU 3072897 A	09-12-1997
		EP 0906417 A1	07-04-1999
		JP 2000514282 T	31-10-2000
		KR 2000015993 A	25-03-2000
		WO 9744445 A1	27-11-1997
		ZA 9704325 A	18-12-1997

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No.

PCT/US 01/49628

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 4334024	A	08-06-1982	US 4400471 A	23-08-1983
WO 9109943	A	11-07-1991	AT 96167 T	15-11-1993
			DE 69004101 D1	25-11-1993
			DE 69004101 T2	24-03-1994
			WO 9109943 A1	11-07-1991
			DK 506866 T3	21-03-1994
			EP 0506866 A1	07-10-1992
			ES 2060360 T3	16-11-1994
			JP 2975109 B2	10-11-1999
			JP 5502791 T	20-05-1993
			US 5837513 A	17-11-1998